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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/798,090 | 03/11/2004 | Ivan Richards | 04-183 (400.147) | 6030 |

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| EXAMINER | |
|---|---|
| BOWMAN, AMY HUDSON | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1635 | |

DATE MAILED: 08/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/798,090 | RICHARDS ET AL. | |
| | Examiner | Art Unit | |
| | Amy H. Bowman | 1635 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *11 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/18/04, 7/8/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The invention of the above claims is drawn to a chemically synthesized double stranded siNA molecule that directs cleavage of a CHRM3 RNA via RNA interference, wherein each strand of said siNA molecule is about 19 to about 23 nucleotides in length, to various modifications of the siNA molecule, and to a pharmaceutical composition comprising the siNA molecule.

At the outset, it is noted that the claims do not recite a specific target nucleotide sequence by SEQ ID NO, but rather refer to the broad genus of CHRM3 sequences.

The claims encompass chemically synthesized double stranded siNA molecules that direct cleavage of any CHRM3 RNA via RNA interference, as well as encompass those that target any CHRM3 homolog or allele known or yet to be discovered from any species of CHRM3, as well as DNA genomic fragments, splice variants or polynucleotide fragments that express proteins that retain CHRM3 -like activity.

Although the specification discloses specific siNA sequences having complementarity to a single CHRM3 sequence of GenBank accession number NM_000740, the specification does not describe siNA molecules directed to any other species of CHRM3 polynucleotides to describe the instantly claimed genus of siNA molecules directed to any CHRM3 gene. Each of the instantly disclosed siNA molecules are targeted to a single sequence, although the claims are drawn to any CHRM3 sequence. It is the structure of each specific siNA molecule that leads to its function with regards to a specific target sequence. One of ordinary skill in the art could not make such oligos to any CHRM3 without knowledge of the sequence. Given the breadth of sequences embraced in the instantly claimed genus, one could not envision the member oligonucleotides that target such a broad genus.

***Priority***

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

In the instant case, the effective filing date of the instant claims is determined to be that of the instant application 10/798,090, which has an effective filing date of 3/11/2004. The instant case 10/798,090 does not receive the benefit of any of the earlier filed priority documents because the instantly recited target, CHRM3, is not disclosed in the specification or claims of the priority applications. Thus, the instant application 10/798,090 is accorded an effective filing date of 3/11/2004.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 36-69 are rejected under 35 U.S.C. 103(a) as being unpatentable over Elbashir et al., in view of Forsythe et al., Sato et al., Tuschl et al. (WO 02/44321), Matulic-Adamic et al. (U.S. 5,998,203), and Morrissey et al. (US 2003/0206887).

The invention of the above claims is drawn to a chemically synthesized double stranded siNA molecule that directs cleavage of a CHRM3 RNA via RNA interference, wherein each strand of said siNA molecule is about 19 to about 23 nucleotides in length, to various modifications of the siNA molecule, and to a pharmaceutical composition comprising the siNA molecule.

Elbashir et al. teach chemically modified 21-nucleotide siRNA duplexes that mediate RNA interference. Elbashir et al. teach a 21-nucleotide siRNA, wherein the first

strand is 100% complementary to a target and contains a 2'-deoxythymidine modified overhang (see figure 8, ref) and the second strand of the duplex is complementary to the first strand. The duplexes taught by Elbashir et al. comprise an antisense and a sense region and are assembled from two separate fragments. The duplex taught by Elbashir et al. does not comprise a full length RNA transcript of said target gene. Elbashir et al. teach 2'-O-methyl modified siRNA duplexes (see page 6881). Elbashir et al. teach that multiple 2'-deoxynucleotide substitutions at the 3' end of the duplex are tolerated. Furthermore, Elbashir et al. teach a duplex wherein all 21 nucleotides of the first strand are hybridized to all 21 nucleotides of the second strand (see figure F, duplex 1). Elbashir et al. teach that a 5'-phosphate group on the target-complementary strand of the siRNA duplex is required for siRNA function (see page 6886, column 2). The 100% modified siRNA duplexes taught by Elbashir et al. are considered to comprise no ribonucleotides.

Elbashir et al. do not teach siNA molecules that direct cleavage of CHRM3 RNA, nor do they teach 2'-deoxy-2'-fluoro modifications, phosphorothioates, abasic moieties, inverted deoxyabasic moieties, glyceryl moieties, linkers, terminal cap moieties, or pharmaceutical carriers or diluents.

Forsythe et al. teach the cDNA encoding the human m3 muscarinic receptor gene. Forsythe et al. isolated and characterized the human m3 muscarinic receptor gene and its promoter.

Sato et al. teach that muscarinic receptor subtype m3 is present on various blood cells, including peripheral lymphocytes. Sato et al. teach that muscarinic receptor

agonists modulate the functions of lymphocytes and that the quantity of muscarinic receptors on lymphocytes is associated with the etiology of some neurological diseases such as Alzheimer's and Parkinson's diseases.

Tuschl et al. teach siRNA duplexes consisting of two separate RNA strands, wherein each strand is 19-25 nucleotides, preferably 21 nucleotides (see pages 3 and 7). The duplexes are capable of mediating RNAi (see page 3). One strand of the duplex is preferably 100% complementary to the target (see page 6). Tuschl et al. teaches targeting of mammalian cells, particularly human cells (see page 4). Tuschl et al. disclose that the dsRNA of their invention can be 21 nucleotide siRNA duplexes with 3' overhangs or with blunt ends wherein the two strands are fully complementary to each other and one strand is fully complementary to at least part of a transcript of a target gene (see page 44, line 25, and figure 11). Tuschl et al. teach that the 5'-terminus preferably comprises a phosphate group (see page 4). The most effective dsRNAs are composed of two 21 nt strands which are paired such that 1-3, preferably 2 nt 3' overhangs are present on both ends of the dsRNA. Tuschl et al. teach chemical modifications at the 5' and/or the 3/ end of the dsRNA molecule (see page 5) for stabilization against degradation. Tuschl et al. teach 2'-deoxy, 2'-O sugar modifications and phosphorothioates. Tuschl et al. teach pharmaceutical compositions comprising the siRNA and a carrier or diluent. Tuschl et al. teach that siRNAs represent a new alternative to antisense or ribozyme therapeutics. Tuschl et al. teach a method of synthesizing siRNA duplexes that are complementary to a pre-selected target.

Matulic-Adamic et al. teach double stranded short interfering nucleic acid molecules that comprise a first nucleotide sequence complementary to a target or a portion thereof, and a second sequence having complementarity to said first sequence. As defined in the instant specification, page 69, the term "siNA" refers to any nucleic acid molecule capable of inhibiting or down regulating gene expression or viral replication, for example by mediating RNAi or gene silencing in a sequence-specific manner. Each of the strands of the siNA taught by Matulic-Adamic et al. is about 19 to about 23 nucleotides in length, as instantly claimed. Matulic-Adamic et al. teach chemical modifications of the double stranded structure. The ribozymes taught by Matulic-Adamic et al. comprise ribonucleotides and cleave other separate RNA molecules in a nucleotide base sequence-specific manner. Such enzymatic RNA molecules are taught to be targeted to virtually any RNA transcript and achieve efficient cleavage (see column 1) and to be sufficiently complementary to a target sequence to allow cleavage. For example, figure 3 contains a ribozyme structure that encompasses modification of the nucleotide positions, as well as the modifications instantly claimed. When 100% of the nucleotide positions are modified, the duplex is considered to comprise no ribonucleotides. The modifications can be in one or both of the strands. Helix 4 can be formed from two separate molecules, i.e. without a connecting loop. When the connecting loop is present, it can be a ribonucleotide or non-nucleotide linker. Matulic-Adamic et al. teach the incorporation of chemical modifications at the 5' and/or 3' ends of the nucleic acids to protect the enzymatic nucleic acids from exonuclease degradation, which improves the overall effectiveness of the nucleic acid, as well as

facilitates uptake of the nucleic acid molecules (see column 2). Matulic-Adamic et al. teach base, sugar and/or phosphate modification, as well as terminal cap moieties at the 5'-cap, 3'-cap, or both. Specifically, 3' phosphorothioates, inverted abasic moieties, and 2'-O-methyl modifications are utilized. Matulic-Adamic et al. teach 2'deoxy nucleotides and 2'-deoxy-2'-halogen nucleotides, wherein Br, CL and F are representative halogens (see column 3, for example).

Morrissey et al. teach terminal glyceryl modification to siNA constructs to preserve RNAi activity in cells and dramatically increase the serum stability of the compound (see page 6).

It would have been obvious to one of ordinary skill in the art to design a siRNA, as taught by Elbashir et al., Tuschl et al, or Matulic-Adamic et al., to direct cleavage of a CHRM3 RNA as taught by Sato et al. One would have been motivated specifically to inhibit CHRM3 because Sato et al. teach that muscarinic receptor subtype m3 is present on lymphocytes and that agonists of muscarinic receptors modulate the functions of lymphocytes. Therefore, one of skill in the art would be motivated to inhibit muscarinic receptor subtype m3 for the benefit of modulating lymphocytes that are associated with the etiology of diseases. Furthermore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate 2'-deoxy-2'-fluoro modifications, phosphorothioates, abasic moieties, inverted deoxyabasic moieties, glyceryl moieties, or terminal cap moieties, as well as linkers or pharmaceutical carriers, as taught by Tuschl et al. and Matulic-Adamic et al. or to incorporate a glyceryl modification as taught by Morrissey et al. One would have been

motivated to incorporate each of these modifications since each of these modifications were known in the art to add beneficial properties to siNA molecules, such as increasing nuclease resistance and stability of the duplex.

Finally, one would have a reasonable expectation of success given that Elbashir et al., Tuschl et al., and Matulic-Adamic et al. each teach designing siNA molecules to direct cleavage of known genes and the cDNA sequence encoding CHRM3 was known in the art, as evidenced by Forsythe et al. For example, Matulic-Adamic et al. teach that such RNA molecules are targeted to virtually any RNA transcript and achieve efficient cleavage (see column 1). Elbashir et al. and Tuschl et al. each teach a method of synthesizing siRNA duplexes that are complementary to a pre-selected target. Additionally, each of the modifications instantly claimed were known in the art to add benefits to siNA molecules, each of which one would reasonably expect to benefit an siNA targeted to CHRM3.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-31 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-31 of copending Application No. 10/919,866. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of each of the applications encompass the same invention.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The instant invention is drawn to a chemically synthesized double stranded siNA molecule that directs cleavage of a CHRM3 RNA via RNA interference wherein each strand is about 19 to about 23 nucleotides in length and one strand of said siNA molecule comprises nucleotide sequence having sufficient complementarity to said CHRM3 RNA for the siNA molecule to direct cleavage of the CHRM3 RNA via RNA interference, and said siNA molecule does not require the presence of nucleotides having a 2' hydroxy group for mediating RNAi. The invention is further drawn to various modifications of the duplex, as well as linker molecules and pharmaceutical compositions.

Application '866 teaches a chemically synthesized double stranded siNA molecule that directs cleavage of a CHRM3 RNA via RNA interference wherein each

strand is about 18 to about 23 nucleotides in length and one strand of said siNA molecule comprises nucleotide sequence having sufficient complementarity to said CHRM3 RNA for the siNA molecule to direct cleavage of the CHRM3 RNA via RNA interference. Application '866, claims 2-31 recite the same exact limitations including various modifications of the duplex, as well as linker molecules and pharmaceutical compositions as instantly claimed. Each strand of the siNA duplexes of application '866 is about 18 to about 23 nucleotides in length, which encompasses the instant limitation of about 19 to about 23 nucleotides in length. Therefore, the instant claims and the claims of application '866 are each obvious over the other in view of the overlapping scope.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy H. Bowman whose telephone number is 571-272-0755.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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Amy H. Bowman
Examiner
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